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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,889	11/28/2000	Bryan Julien	300622003111	7394

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EXAMINER

NASHED, NASHAAT T

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 01/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/724,889	JULIEN ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Nashaat T. Nashed	1652	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE \_\_\_\_ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 October 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☐ Claim(s) \_\_\_\_ is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 15-17, 25 and 29-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11/28/00 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \*   c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                            | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____   |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)        | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ | 6) <input type="checkbox"/> Other: _____                                    |

The application has been amended as requested in the communication filed October 22, 2003. Accordingly, claims 15, 16, 25, and 29-34 have been amended; and claims 29-34 have been entered.

Claims 15-17, 25, and 29-34 are under consideration.

Applicants continue to traverse the restriction requirement which has been traversed and made final in the previous Office action mailed May 22, 2003. The examiner does not have any further comment on the restriction requirement.

This application appears to have been filed with informal drawings which are acceptable for examination purposes only. The drawing of low quality. Formal drawings are required.

In response to the above objection to the specification, applicants indicated that a new set of drawing will be filed with a future amendment.

Applicant response to the previous Office action mailed on May 22, 2003 with regard to the drawing is considered a *bona fides* attempt to respond to the Office action. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-17, 25, 30, 31, and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

- (a) Claim 15 is directed to "a modified epothilone synthase", i. e., a singular protein. Thus, the clause "wherein the modified PKS produces an epothilone derivative" renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. From reading the specification, the examiner comes to the conclusion that, at least, five polyketide synthases are required for the synthesis of the macrolactone structure or epothilone D derivatives. For examination purposes only, the examiner assumed that the modified epoE is capable of producing epothilone D derivatives in the presence of EpoA, EpoB, EpoC, and EpoD.
- (b) Claim 29 is directed to "a modified epothilone synthase", i. e., a singular protein. Thus, the clause "said PKS comprising (a) ...., and (b) " renders the claim

indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes only, it is assumed that the claim reads on modified functional epoE comprised in a non-*S. cellulorum* containing epoA, epoB, .....and epoF, wherein said host cell produces an epothilone D derivatives.

- (c) Claims 16, 17, and 30-34 are included with these rejections because they are dependent on a rejected claim and do not cure its deficiencies.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18, 25, and 29-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the prior Office action mailed May 22, 2003.

Applicants have not traversed or obviated this rejection in the response to the office action. For applicants convenience, the rejection is reiterated below.

Claims 15-18 and 29-34 are directed to modified epoE, the product of the *epoE* gene, isolated from any biological source have any structure. Claim 25 is directed to any polyketide synthase comprising the methyl transferase domain of presumably module 8 of epoE. The specification, however, only provides a single representative species of the epoE from *Sorangium cellulosum* encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these epoE by any identifying structural characteristics or properties other than the enzymatic activities recited in the table on page 52 and the nucleic acid encoding said activities listed in the table on pages 14 and 15, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 15-17, 25 and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schupp *et al.* (Schupp, IDS paper number 13, Ref.No. 5, U. S. Patent 6,355,459) in view Khosla *et al.* (Khosla A, IDS reference, paper number 10, reference number 10, U. S. Patent 6,391,594), and Khosla *et al.* (Khosla B, IDS paper number 11, Ref No. 33: WO 97/02358).

In response to the above rejections, Applicants argue that several teachings of Schupp are erroneous including that the C-12 methyl group in epothilone B requires a non-epothilone gene cluster methyltransferase. In addition, they have not mentioned the compound epothilone D.

Applicants' arguments filed 10/22/03 have been fully considered but they are not deemed to be persuasive. While it is true that Schupp do not teach the chemical compound epothilone D by name in the specification and contains some errors regarding some chemical steps, they teach epothilone derivative of epothilone D, i. e., epothilone A and epothilone B, see column 2, lines 25-45. Also, Schupp teach the expression of epothilone genes in a non-*S. cellulosum* cell, including *S. coelicolor*, see examples 13 and 14, and the production of epothilone A and epothilone B. Clearly, the results of Schupp show that a substantial amount of epothilone B is formed and, in many instances, more epothilone B is formed than epothilone A. The fact that epothilone B is made under the fermentation conditions of Schupp indicates that epothilone D must have been formed during the fermentation. It should be noted that one of ordinary skill in the art would consider both epothilone A and epothilone B derivatives of epothilone D. In addition, since the claim is directed to modified epothilone polyketide synthase wherein the acyl transferase domain in module 7 and/or 8 are replaced by another acyltransferase domain having different activity which would lead to the formation of any epothilone D derivative which include variants of epothilone A and epothilone B, the claims are not limited to those formed from epothilone D precursor. Schupp teach that epoF is a P-450 enzyme, and suggested that epoF adjust the redox state at C-3, C-5, and C-12. That includes epoxide ring formation by the addition of one oxygen atom to the double bond between C12 and C13 which is a well established reaction for P-450 monooxygenases. In contrast, oxidation of hydroxyl groups are not reactions catalyzed by P-450 monooxygenases.

Thus, One of ordinary skill in the art would have modified the epoE gene product as being claimed by well known methods in the art, construct a host cell comprising the modified PKS and the other protein product of the epothilone gene cluster and make novel epothilone derivatives as taught by Schupp. The claims remain rejected for the above reasons.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Nashaat T. Nashed, Ph. D.  
Primary Examiner